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10/509,799	07/15/2005	Yoshiki Sawa	Anges-5	3108

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,799	SAWA ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-12 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on March 2, 2007 is acknowledged.

Applicant has elected the decoy species "NFκB" and the disease/disorder species "brain ischemia".

2. Election of Applicant's invention(s) was made without traverse. Because applicant did not distinctly and specifically point out the supposed errors in the species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

3. Claims 3 and 13 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-2, 4-12 and 14-20 are under consideration.

Priority

5. This application is a 371 of PCT/JP02/03239, filed March 29, 2002. Applicant's claim for the benefit of a prior-filed application parent application PCT/JP02/03239 under 35 U.S.C. under 35 U.S.C. §120 or §365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on September 29, 2004 and July 3, 2006 that have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

The information disclosure statement filed July 3, 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citation of Sawa et al, 1997 is incomplete. In particular, page II-284 is absent. Because Sawa et al cite references that more fully describe their compositions and methods of using said compositions, page II-284 is directly relevant for providing the necessary bibliography.

It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Drawings

6. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawings filed September 29, 2004 prevent the Examiner from evaluating the data on its merits. The provided reproductions of Figure 1 are essentially opaque, and the image resolution of panels A-1 and A-2 of Figures 3 and 4 fail to reproduce well. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a broad genus of polynucleotide sequences (NFκB decoys) that specifically bind to NFκB such that NFκB-regulated genes are competitively inhibited, and methods of using said polynucleotides for the prevention and treatment of a broad genus of diseases or disorders associated with ischemia of the brain in an enormous genus of vertebrate and invertebrate organisms (pg 34, lines 15-19).

At issue for the purpose of written description requirements is the lack of written description regarding the structure/function relationship as it relates to the breadth of the claimed NFκB decoys so as to achieve the claimed therapeutic results. When the claims are analyzed in light of the specification, instant invention recites/encompasses an enormous genus of structurally distinct nucleic acids having therapeutic activity.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The instant invention recites administration of decoy molecules comprising NFκB binding sequences such that NFκB-regulated genes are competitively inhibited. Multiple binding sequences are contemplated, such as non-replicative oligonucleotides of at least 6-8 base pairs, the 5' non-coding region of said genes, a consensus sequence, sequences flanked by cis-element flanking regions or naturally occurring sequences. In analyzing whether the written description

requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NO:1 is the only NFκB decoy species whose complete structure is disclosed.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the oligonucleotide may contain mutants thereof (SEQ ID NO:1), may be either DNA or RNA, may include a modified nucleic acid and/or pseudo-nucleic acid may be single-stranded or double-stranded, or may be linear or circular. The mutants are nucleic acids having the above-described sequences, a part of which has a mutation, a substitution, an insertion, or a deletion, and which specifically antagonizes a transcription factor (pgs 15-16, joining ¶). **In regard to NFκB decoys from species other than humans, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had the same characteristics or would have had additional characteristics or properties.** It is noted that all these NFκB decoys vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicants have not provided the structural requirements of a decoy that must meet the contemplated therapeutic functional limitations and have not demonstrated that it was conventional in the art to do so. The specification does not reduce to practice the ability to identify NFκB decoys besides SEQ ID NO:1 and the ability to determine *a priori* whether a molecule will function as recited is highly unpredictable. Nor has a structure-function relationship been provided. Therefore, the instant specification hasn't provided a structural/

functional basis for the skilled artisan to envision a broad genus of decoys. Given the diversity of known *cis*-acting NFκB binding sites within the genome, and the inability to determine which will also possess the ability to function as "decoys" to completely inhibit binding of NFκB to the genes it regulates, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

The one species of NFκB decoys specifically disclosed, SEQ ID NO:1, is not representative of the genus because the genus is highly variant. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the NFκB decoys as defined by the specification and encompassed by the claims to fulfill the required therapeutic purposes so as to perform the claimed method(s). Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of NFκB decoys, besides SEQ ID NO:1 at the time the application was filed. It naturally follows that the Applicant is not in possession of the required starting materials, that is the broad genus of NFκB decoys, to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that Claims 1-2, 4-12 and 14-20 do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 112, first paragraph,** because the specification, while being enabling for a composition comprising a NFκB decoy consisting of the nucleic acid sequence of SEQ ID NO:1 and a method of treating brain ischemia in a mammal comprising the step of administering a NFκB decoy consisting of the nucleic acid sequence of SEQ ID NO:1, does not reasonably provide enablement for:

i) a broad genus of structurally diverse polynucleotide NFκB decoy sequences,

ii) formulating said broad genus of NFκB decoy polynucleotides to be appropriate for an enormous genus of administration routes, including a carotid artery, and

iii) methods of preventing an enormous genus of etiologically and pathologically distinct diseases or disorders associated with an ischemic condition of a brain in an enormous genus of animal organisms using the broad genus of recited NFκB decoy composition(s).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

In the broadest sense, the invention(s) read on the synthesis of an enormous genus of structurally diverse polynucleotide sequences to be used for the prevention and treatment of an enormous genus of etiologically and pathologically distinct disease states in an enormous genus of vertebrate and invertebrate organisms (pg 34, lines 15-19), including humans, through the introduction of double-stranded NFκB oligonucleotide decoys.

The art recognizes that invertebrate animals comprise as much as 97% of all known animal species on the planet, including sponges, worms, squid, and insects. Even within vertebrates, about 57,739 species have been described (en.wikipedia.org/wiki/vertebrates, last visited April 24, 2007).

The instant disclosure is directed to the broad field of decoy therapy. Decoy therapy is based upon blocking the capacity of endogenous trans-activating factors to modulate gene expression and thereby affecting the pathological processes associated with the transcription factors. The invention recites a method for the modulation of gene transcription by delivering an NFκB decoy *in vivo* into a cell for modulating gene transcription. The invention utilizes disciplines of molecular biology and gene therapy. The decoy nucleic acid comprises a binding sequences that is broadly disclosed as any sequence that specifically binds to a transcription factors such as non-replicative oligonucleotides of at least 6-8 base pairs, the 5' non-coding region of said genes, a consensus sequence, sequences flanked by cis-element flanking regions or naturally occurring sequences.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The art recognizes that transcription factor decoys represent a novel class of therapeutic agents that may possess tremendous potential for entirely new opportunities in targeted molecular disease intervention. Transcription factor decoys are molecules that mimic the binding sites for transcription factor proteins, and compete with promoter regions to absorb this binding activity in the cell nucleus. By blocking transcription factor– chromosomal DNA interaction, these molecules provide a powerful means to manipulate the regulation of gene expression, particularly as transcription factors are increasingly understood to alter gene activation during the course of normal and pathologic processes in cell biology (Mann, Ann. N.Y. Acad. Sci. 1058:128-139, 2005; Abstract). To date, most transcription factor decoys that have been studied have comprised double-stranded DNA oligonucleotides that contain either one copy or a tandem repeat of a sequence representative of the consensus binding sequence recognized by the target transcription factor (Mann, 2005, pg 129, ¶1). The multiplicity of transcription factors that

regulate a given gene and the multiplicity of target genes that are under control of a single transcription factor represent important limitations to the decoy ODN strategy. Specificity becomes an even greater challenge when target gene expression is to be inhibited only in a single organ or tissue type (Mann, J. Clinical Invest. 106(9):1071-1075, 2000; pg 1074, col.s 1-2, joining ¶).

Delivery and Pharmacology

The use of synthetic ODNs as drugs is a relatively new concept in the field of pharmacology. Indeed, several studies involving oligonucleotide-based therapeutics are already in the preclinical or clinical stages of development. The key objective in the field, however, remains the identification of oligonucleotide analogs providing high *in vivo* efficacy. (Crinelli et al, Nucleic Acids Res. 32(6):1874-1885, 2004; pg 1882, col. 2, Discussion). A significant challenge facing the clinical implementation of a transcription factor decoy strategy lies in the effective delivery of the macromolecules to cells with in intact tissues *in vivo* (Mann, 2005; pgs 131-132, joining sentence). Naked decoy oligonucleotides do not benefit from the complex machinery available to viral gene transfer constructs both for crossing the cell membrane and for gaining entry to the cell nucleus where the transcriptional machinery resides. In fact, most oligonucleotide cell uptake is believed to progress via an endocytotic process in which much of the active oligonucleotide undergoes lysosomal degradation. However, modifications introduced into oligonucleotides to increase stability quite often do not guarantee that transcription factor affinity and/or specificity of recognition are retained (Crinelli et al; Abstract). The requirements for structural modifications to improve the pharmacological properties of a DNA molecule, as per increased nuclease resistance and high target affinity, are difficult to reconcile in a decoy ODN, where the ideal modification should, on the one hand, prevent nuclease degradation and, on the other, preserve the molecular interactions with the target transcription factor, in order to retain both the affinity and the specificity of recognition. Despite impressive gains in structural biology over the past years, the effects produced by nucleotide modification on DNA/protein interactions are still difficult to predict (Crinelli et al; pg 1875, col. 1, ¶1).

In general, the use of decoy molecules for the treatment of disease depends on several factors including cellular uptake efficiency, intracellular stability, cellular toxicity and non-

specific effects (Bene et al, Nucleic Acids Research 32(19): e142, pages 6/6, 2004; e.g. page 1/6, paragraph bridging columns). Bene et al teach that electrophoretic mobility shift assays and reporter assays performed *in vitro* are insufficient to determine the specificity of the decoy to localize to the nucleus and block transcriptional activity *in vivo* (e.g. page 1/6, right column, ¶1). Further, Bene et al demonstrate that specific binding *in vitro* coupled with efficient uptake by cells (80% efficiency) was insufficient to affect inhibition of transcription factor activity by an AP-1 decoy composition (e.g. pages 4/6-5/6, Results and Discussion). Many studies of decoy ODNs have not reported subcellular localization and have not demonstrated specific inhibitory effects on transcription. Therefore, the reported biological effects may be non-specific in nature. Bene et al suggest that the lack of an effect was due to the cytosolic localization of the AP-1 decoy molecule (e.g. page 4/6, right column, ¶1).

At the time of filing, March 29, 2002, decoy gene therapy was, and remains, a developing art, and the unpredictability of using this invention was, and remains, high due to the lack of methods or processes for its use *in vivo*. Many parameters had not been addressed, such as which dsDNA molecule to use, the amount of DNA to be delivered, the timing of administration, retention, and the stability of the decoy *in vivo*. The few *in vitro* assays with an NFκB binding element provided evidence in the prior art that decoy use *in vitro* has promise. However, *in vitro* and animal models have not correlated well with *in vivo* clinical trial results in human patients. Since the therapeutic indices of NFκB decoy molecules can be species- and model-dependent, it is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy. To date, the process of treating and preventing disease in humans remains highly unpredictable by any method.

NFκB

NFκB is a particularly attractive target since it has been implicated as a master switch not only in driving the cellular response to pro-inflammatory stimuli, but to intra- and extra-cellular stresses in general. Like many transcription factors, there is a family of NFκB-related proteins, grouped generally into the 5 subclasses of NF-B1 (p50/p105), NF-B2 (p52/p100), RelA (p65), RelB, and c-Rel. The active NFκB moiety is either a homodimer or heterodimer made up of these individual subunits. An opportunity therefore exists to optimize the inhibitory effect of an

NFκB decoy by targeting relative differences in affinity of p65 hetero- and homodimers exhibited by different oligonucleotide sequences (Mann, 2005; pg 133).

Several prior art references teach the use of an exceptionally small sub-genus of NFκB decoys *in vivo* in a variety of animal models in contrast to the enormous genus of structurally diverse nucleic acid sequences for use a pharmaceutical agents embraced by the instant claims. The prior art teaches that RNA decoys may be selected for NFκB binding, and that DNA or 2'-O-methyl RNA analogs of the same sequence were unable to bind NFκB (Lebruska et al, Biochemistry 38(10):3168-3174, 1999; e.g. Abstract, page 3171). The instant specification does not provide a set of sequences that may be used as DNA or RNA decoys to prevent NFκB binding to transcription factor sites clinically relevant for the recited disease states.

In fact, the art teaches that decoy activity may be cell-type specific and administration specific. Anti-inflammatory responses of NFκB decoys are proposed to occur through modulation of NFκB mediated events. However, topical lung administration of NFκB decoys was not capable of modulating NFκB events. Rather, the decoys did not elicit anti-inflammatory responses in the airways or modulate of IL-6 expression. The lack of positive results was thought to be a product of cytoplasmic accumulation of the decoy (Griesenbach et al, Gene Therapy 9(16):1109-1115, 2002; pg 1112, col. 2). In other results, Abeyama et al (J. Clin. Invest. 105(12): 1751-1759, 2000) compared results using intraperitoneal injection of decoys versus topical application. While, topical application resulted in reversal of NFκB mediated events related to dermatitis, intraperitoneal injection did not (see e.g. page 1755, col 1). Bene et al (discussed above) and Griesenbach et al teach the unpredictability of delivering NFκB decoy molecules to the nucleus and thus the unpredictability of obtaining an effect on transcriptional activity. Therefore, the recited claims are highly unpredictable given the lack of predictability of identifying the proper means and decoys and cell types which will elicit therapeutic effects on dermatitis. The claims do not identify the cell type or means of administration. To the contrary, the specification teaches only that specific cells are treated by specific administration of a specific decoy with specific vehicle. This position of unpredictability is supported by the art, which teaches that particular cells require particular means of application.

The MPEP teaches,

"However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b).

The lack of well-defined targets (i.e. what genes are to be modulated) compounded by the lack of disclosure of the actual decoys besides SEQ ID NO:1 to be used or direct guidance directed towards the identification NFκB decoys makes use of the method for modulating gene transcription *in vivo* highly unpredictable. Given the disclosure, it would require undue experimentation to identify the NFκB decoy given the broad and undefined nature of the gene target. The cited references teach how to make and use linear, double-stranded NFκB decoy molecules to inhibit NFκB binding. The references do not teach the use of single-stranded DNA or RNA decoys, for example. Further, the references do not teach which NFκB binding sites are clinically relevant for treating an enormous genus of inflammatory and articular diseases and disorders, such that one could design additional double-stranded NFκB decoy molecules. The art recognizes that the sequences of NFκB binding sites are simply not known in the enormous genus of invertebrate and vertebrate animals reasonably embraced by the claims. Applicant presents no art-recognized nexus between the results obtained in the prior art with the specific NFκB decoy nucleic acids in the few animal models and the results the skilled artisan would expect to see in the enormous genus of invertebrate and vertebrate animals reasonably embraced by the claims.

Disease Prevention

The claimed inventions recite methods of preventing an enormous genus of diseases and disorders associated with an ischemic condition of the brain. Applicant has presented no art-recognized nexus between the results obtained in laboratory animal models and the results the skilled artisan would expect to see in humans. Furthermore, none of the animal models demonstrate prevention of ischemic conditions. In humans, the claimed diseases are usually

established before therapy is offered. The specification does not adequately teach how to effectively predict for whom the prevention would be required. In view of the predictability of the art to which the invention pertains, and the lack of established clinical protocols to predict for whom the therapies would be required, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description by Applicant how to reasonably determine which population the claimed invention is intended.

Pharmaceutical Formulary Adaptation

The art is silent with respect to the necessary guidance for adapting a therapeutic composition for administration to an enormous genus of administration routes (pg 17, lines 28-33), including the carotid artery, to the enormous genus of contemplated animals, including invertebrates such as *Drosophila melanogaster* (fruit fly), spiders and scorpions, as well as vertebrates such as snakes, fish, frogs, turtles and tortoises, birds, and the enormous genus of mammalian animals. For example, Applicant contemplates oral delivery of the pharmaceutical composition for the treatment of brain ischemia, but has disclosed no formulary to guide the artisan how much of the composition is required to achieve a therapeutically effective and preventive amounts when the composition must be absorbed by the gastrointestinal system before entering the circulatory system. The art recognizes that each of these organisms are physiologically and pathologically distinct, and Applicant has provided no teachings so as to guide an artisan to adapt the inventive composition for the enormous genus of administration routes to the enormous genus of invertebrate and vertebrate organisms reasonably embraced by the claims. In the absence of the required information, one of ordinary skill in the art would reasonably conclude significant unpredictability because one cannot predict what one does not know.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

Pharmaceutical Formulation

Applicants disclose a single NFκB decoy having the nucleic acid sequence of SEQ ID NO:1 and disclose a working example using said decoy in an animal model of artificially-

induced global ischemia. However, the claims recite a broader genus of nucleic acids having therapeutic activity. The specification discloses that the only other identifying characteristic of a therapeutic NFκB decoy is that the oligonucleotide may contain mutants thereof (SEQ ID NO:1), may be either DNA or RNA, may include a modified nucleic acid and/or pseudo-nucleic acid may be single-stranded or double-stranded, or may be linear or circular. The mutants are nucleic acids having the above-described sequences, a part of which has a mutation, a substitution, an insertion, or a deletion, and which specifically antagonizes a transcription factor (pgs 15-16, joining ¶). The teachings of the instant specification, and the prior art, do not provide structural/functional relationships that would allow one to vary the sequence of the NFκB decoy (e.g. other NFκB binding sites) *a priori* and maintain the ability to treat the enormous genus of diseases and disorders associated with ischemic conditions of the brain.

Methods of Use

The instant specification discloses, "Guidance for specific doses and delivery methods are provided in publications known in the art." (pg 28, lines 27-28) "[A]ny route may be possible as long as the composition is delivered through the route to a site to be treated, i.e., brain." (pg 18, lines 1-3) "A therapeutically effective dose of any compound can be initially estimated using either a cell culture assay or any appropriate animal model. The animal model is used to achieve a desired concentration range and an administration route." (pg 27, lines 11-15). This guidance is general and broad for the use of NFκB decoys to the enormous genus of contemplated inflammatory and articular diseases and disorders. This paucity of information in no way provides the skilled artisan with the ability to use the decoy(s) as per the claimed methods. The specification provides a single working example using the decoy of SEQ ID NO:1 in macaques (Example 1), wherein the decoy composition was complexed with HVJ-liposomes and suspended in a balanced saline solution (pg 49) and administered directly into the carotid artery (pg 50, line 30). Therefore, the teaching of the specification and the dearth of knowledge in the prior art do not teach one how to use the NFκB decoys for therapeutic purposes in the enormous genus of invertebrate and vertebrate organisms. It is noted that the administration of naked NFκB decoys into the carotid artery did not yield transfected brain cells (pg 51, lines 24-28). Rather, transfection required the HVJ-liposome complex.

Furthermore, the claims recite methods of prevention. However, the specification fails to disclose guidance teaching an artisan how to prevent the occurrence of each of the diseases or conditions in the enormous genus of organisms. Therefore, disease prevention is highly unpredictable as it is unclear for whom the treatment is targeted, the sites of administration, the intended therapeutic product and the intended target organ(s).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the enormous genus of claimed NFκB decoy nucleic acid molecules may be adapted for any administration route to an enormous genus of physiologically and pathologically distinct invertebrate and vertebrate organisms for the prevention or treatment of an enormous genus of etiologically distinct diseases and disorders associated with ischemia of the brain and for the gene transfection of brain cells of said organisms.

The invention recites a complex series of steps of designing, synthesizing, formulating and delivering an NFkB decoy in a form permitting cellular internalization into the nucleus to competitively inhibit NFkB binding to its target gene(s). The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art. Given the very large genus of decoy molecules encompassed by the claims, and given the limited description provided by the prior art and specification with regard to the structure and function of decoy molecules capable of treating an enormous genus of diseases and disorders associated with ischemia of the brain, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those decoy molecules that satisfy the functional limitations of the claims.

In view of unpredictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be

required, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a composition comprising a NFκB decoy consisting of the nucleic acid sequence of SEQ ID NO:1 and a method of treating brain ischemia in a mammal comprising the step of administering a NFκB decoy consisting of the nucleic acid sequence of SEQ ID NO:1, is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(a)** as being anticipated by Yokoseki et al (Circulation Res. 89(10):899-906, 2001; available online September 27, 2001).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Yokoseki et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 900, Materials and Methods).

With respect to Claims 4 and 10, Yokoseki et al teach the encapsulation of the NFκB decoy oligonucleotide into an HVJ-liposome (pg 900, col. 1, DNA Sequences and Liposomes).

With respect to Claim 5, Yokoseki et al teach the NFκB decoy oligonucleotide comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 900, col. 1, DNA Sequences and Liposomes).

With respect to Claim 6, Yokoseki et al teach the NFκB decoy composition to comprise 15μmol/L of the decoy in balanced saline solution (pg 900, col. 1, DNA Sequences and Liposomes). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Yokoseki et al anticipate Claims 1-2 and 4-10.

10. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 102(a)** as being anticipated by Ueno et al (J. Thorac. Cardiovasc. Surg. 122:720-727, 2001; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an

ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7, 9, 11-12, 17 and 19, Ueno et al disclose a pharmaceutical composition comprising at least one NFκB decoy and a pharmaceutically acceptable carrier for the therapy and prophylaxis of various NFκB-associated diseases, e.g. ischemic brain diseases (pg 720, Objectives). Ueno et al teach that introduction of the NFκB decoy into rat brain neurons through the carotid artery during global brain ischemia was markedly successful (pg 720, Results).

With respect to Claims 4, 10, 14 and 20, Ueno et al teach pharmaceutically acceptable carriers, including the carrier to be a liposome suspended in balanced saline solution (pg 721, col. 1, Liposome).

With respect to Claim 5 and 15, Ueno et al teach at least one NFκB decoy, wherein SEQ ID NO:1 comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 721, col. 2, line 4).

With respect to Claims 6, 8, 16 and 18, Ueno et al teach, for example, the formulated NFκB decoy composition to be dissolved in balanced saline solution, wherein the composition is injected into the carotid artery (pg 721, col. 2, Ischemia Model). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Ueno et al anticipate Claims 1-2, 4-12 and 14-20.

11. **Claims 1-2 and 6-9 are rejected under 35 U.S.C. 102(a)** as being anticipated by Blondeau et al (J. Neurosci. 21(13): 4668-4677, 2001; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an

ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2 and 7-9, Blondeau et al teach a pharmaceutical composition comprising at least one NFκB decoy and a pharmaceutically acceptable carrier for the therapy and prophylaxis of various NFκB-associated diseases, e.g. ischemic brain diseases (pg 4669, col. 1, Forebrain Ischemia).

With respect to Claims 6, Blondeau et al teach the formulated NFκB decoy composition to be dissolved in saline solution (pg 4669, col. 2, Decoy Administration). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Blondeau et al anticipate Claims 1-2 and 6-9.

12. **Claims 1-2, 4 and 6-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Miagkov et al (Proc. Natl. Acad. Sci. 95(23):13859-13864, 1998).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Miagkov et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 13860, col. 1, Materials and Methods).

With respect to Claims 4 and 10, Miagkov et al teach the encapsulation of the NFκB decoy oligonucleotide into a DOTAP liposome (pg 13860, col. 1, Decoys).

With respect to Claim 6, Miagkov et al teach the NFκB decoy composition to be dissolved in saline buffer. To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but

does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Miagkov et al anticipate Claims 1-2, 4 and 6-10.

13. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Morishita et al (Nature Medicine 3(8):894-899, 1997; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Morishita et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 898, Materials and Methods).

With respect to Claims 4 and 10, Morishita et al teach the encapsulation of the NFκB decoy oligonucleotide into a HVJ liposome (pg 898, col. 1, Liposome).

With respect to Claim 5, Morishita et al teach at least one NFκB decoy, comprising a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 897, col. 2, Synthesis of ODN).

With respect to Claim 6, Morishita et al teach the NFκB decoy composition to comprise an equivalent of 15μM of the decoy in balanced saline solution (pg 898, col. 1, Liposomes). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Morishita et al anticipate Claims 1-2 and 4-10.

14. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Tomita et al (Arth. and Rheum. 42(12):2532-2542, 1999).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Tomita et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 2533, Materials and Methods).

With respect to Claims 4 and 10, Tomita et al teach the encapsulation of the NFκB decoy oligonucleotide into a HVJ liposome (pg 2533, col. 1, Liposome).

With respect to Claim 5, Tomita et al teach at least one NFκB decoy, comprising a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 2533, col. 1, Synthesis of ODN).

With respect to Claim 6, Tomita et al teach the NFκB decoy composition to comprise an equivalent of 15μM of the decoy in balanced saline solution (pg 2533, col. 2, Materials and Methods). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Tomita et al anticipate Claims 1-2 and 4-10.

15. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Tomita et al (Gene Therapy 7(15):1326-1332, 2000; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an

ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 1330, Materials and Methods).

With respect to Claims 4 and 10, Tomita et al teach the encapsulation of the NFκB decoy oligonucleotide into an HVJ-liposome (pg 1330, col. 2, Liposome).

With respect to Claim 5, Tomita et al teach the NFκB decoy oligonucleotide comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 1330, col. 1, Synthesis of ODN).

With respect to Claim 6, Tomita et al teach the NFκB decoy composition to comprise 3μM, 6μM or 30μM of the decoy in balanced saline solution (pgs 1330-1331, Materials and Methods). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Tomita et al anticipate Claims 1-2 and 4-10.

16. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Tomita et al (Rheumatology 39(7):749-757, 2000; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Tomita et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 750, Materials and Methods).

With respect to Claims 4 and 10, Tomita et al teach the encapsulation of the NFκB decoy oligonucleotide into a HVJ liposome (pg 750, col. 2, Liposome).

With respect to Claim 5, Tomita et al teach at least one NFκB decoy, comprising a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 750, col. 1, Synthesis of ODN).

With respect to Claim 6, Tomita et al teach the NFκB decoy composition to comprise 15μM of the decoy in balanced saline solution (pg 751, col. 1, Liposomes). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Tomita et al anticipate Claims 1-2 and 4-10.

17. **Claims 1-2 and 4-10 are rejected under 35 U.S.C. 102(b)** as being anticipated by Sawa et al (Circulation 96(6):280-285, 1997; *of record).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition.

With respect to Claims 1-2, 7-9, Sawa et al teach a composition comprising at least one NFκB decoy oligonucleotide and a pharmaceutically acceptable carrier (pg 281, Materials and Methods).

With respect to Claims 4 and 10, Sawa et al teach the encapsulation of the NFκB decoy oligonucleotide into an HVJ-liposome (pg 281, col. 1, Liposome).

With respect to Claim 5, Sawa et al teach the NFκB decoy oligonucleotide comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 281, col. 1, Synthesis of ODN).

With respect to Claim 6, Tomita et al teach the NFκB decoy composition to comprise balanced saline solution (pg 281, Materials and Methods, see cited references therein). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Thus, Sawa et al anticipate Claims 1-2 and 4-10.

18. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 102(b)** as being anticipated by Sakaguchi et al (Ann. Thorac. Surg. 71(2):624-630, 2001; available online February 5, 2001).

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition. The claims are also drawn to methods for treating and preventing brain ischemia, comprising the administration of an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier.

With respect to Claims 1-2, 7, 9, 11-12, 17 and 19, Sakaguchi et al disclose a pharmaceutical composition comprising at least one NFκB decoy and a pharmaceutically acceptable carrier for the therapy and prophylaxis of various NFκB-associated diseases, e.g. ischemia-reperfusion injury (pg 624, col. 1, ¶2).

With respect to Claims 4, 10, 14 and 20, Sakaguchi et al disclose pharmaceutically acceptable carriers, including the carrier to be a liposome (pg 625, col. 1, Liposome).

With respect to Claim 5 and 15, Sakaguchi et al disclose at least one NFκB decoy comprising a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 624, col. 2, ODN; see cited references therein).

With respect to Claims 6, 8, 16 and 18, Sakaguchi et al disclose, for example, the formulated NFκB decoy composition to be dissolved in buffered saline solution, wherein the composition may be injected intravascularly, e.g. ascending aorta (pg 625, col. 1, Ex Vivo

Transfer). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Sakaguchi et al do not explicitly teach a method of treating brain ischemia, or a method for carrying out gene transfection in a brain by a route other than direct administration to the brain. However, because Sakaguchi et al performed the method step of inducing ischemia in the heart via cardiac arrest, the brain would inherently and necessarily have experienced ischemia, as there would have been no blood flow to the brain. Similarly, because Sakaguchi et al performed the method step of administering the NFκB decoy into the ascending aorta, which directly leads to the carotid artery, which directly leads to the brain, absent evidence to the contrary, the decoy composition would inherently have treated the brain ischemia and transfected the brain cells.

Thus, Sakaguchi et al anticipate Claims 1-2, 4-12 and 14-20.

19. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 102(b) and 102(e)** as being anticipated by Morishita et al (U.S. Patent No. 6,262,033).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition. The claims are also drawn to methods for treating and

preventing brain ischemia, comprising the administration of an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier.

With respect to Claims 1-2, 7, 9, 11-12, 17 and 19 Morishita et al disclose a pharmaceutical composition comprising at least one NFκB decoy and a pharmaceutically acceptable carrier for the therapy and prophylaxis of various NFκB-associated diseases, e.g. ischemic brain diseases (col. 1, lines 62-64).

With respect to Claims 4, 10, 14 and 20 Morishita et al disclose a genus of pharmaceutically acceptable carriers (col. 3, lines 1-12), including the carrier to be a liposome (col. 3, lines 1-57).

With respect to Claim 5 and 15, Morishita et al disclose at least one NFκB decoy, wherein SEQ ID NO:1 comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC.

With respect to Claims 6, 8, 16 and 18, Morishita et al disclose, for example, the formulated NFκB decoy composition to be dissolved in buffered saline solution, wherein the composition may be injected intravascularly or into the regional blood vessel in the affected region (col. 4, lines 33-36; col. 5, Example 2). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g. physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline (pg 49, Example 1) prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Morishita et al do not explicitly teach a method for carrying out gene transfection in a brain by a route other than direct administration to the brain. However, because Morishita et al contemplate the method step of administering the NFκB decoy intravascularly or into the regional blood vessel in the affected region, which reasonably embraces injection into the carotid artery that directly leads to the brain, absent evidence to the contrary, the decoy composition would inherently have transfected the brain cells.

Thus, Morishita et al anticipate Claims 1-2, 4-12 and 14-20.

20. **Claims 1-2, 4-12 and 14-20 are rejected under 35 U.S.C. 102(b) and 102(e)** as being anticipated by Morishita et al (EP 0-824-918-A1; *of record).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a composition comprising an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier. The intended use of the composition to treat or prevent an ischemic condition of a brain, is not considered limiting, as such use does not confer structural limitations onto the composition. The claims are also drawn to methods for treating and preventing brain ischemia, comprising the administration of an NFκB oligonucleotide decoy and a pharmaceutically acceptable carrier.

With respect to Claims 1-2, 7, 9, 11-12, 17 and 19 Morishita et al disclose a pharmaceutical composition comprising at least one NFκB decoy and a pharmaceutically acceptable carrier for the therapy and prophylaxis of various NFκB-associated diseases, e.g. ischemic brain diseases (pg 2, lines 35-40).

With respect to Claims 4, 10, 14 and 20 Morishita et al disclose a genus of pharmaceutically acceptable carriers (col. 3, lines 1-12), including the carrier to be a liposome (pg 3, lines 17-56).

With respect to Claim 5 and 15, Morishita et al disclose at least one NFκB decoy, wherein SEQ ID NO:1 comprises a nucleotide sequence that is 100% identical to the instantly recited GGATTTCCC (pg 2, line 54; pg 4, line 40)

With respect to Claims 6, 8, 16 and 18, Morishita et al disclose, for example, the formulated NFκB decoy composition to be dissolved in buffered saline solution, wherein the composition may be injected intravascularly or into the regional blood vessel in the affected region, e.g. carotid artery (pg 4, line 21; Example 2; pg 5, lines 1-5; Example 3). To the extent that the instant specification fails to disclose how to formulate the composition so as to be "appropriate" for administration to a carotid artery, but does disclose appropriate solvents, e.g.

physiological saline, phosphate buffered saline, and sterilized water (pg 26, lines 5-8) and teaches a working example wherein the decoy composition is dissolved in saline prior to administration to a rodent carotid artery, the Examiner interprets the dissolving of the decoy nucleic acid into a saline solution to fulfill the "appropriate" limitation.

Morishita et al do not explicitly teach a method for carrying out gene transfection in a brain by a route other than direct administration to the brain. However, because Morishita et al contemplate the method step of administering the NFκB decoy intravascularly or into the regional blood vessel in the affected region, which reasonably embraces injection into the carotid artery that directly leads to the brain, absent evidence to the contrary, the decoy composition would inherently have transfected the brain cells.

Thus, Morishita et al anticipate Claims 1-2, 4-12 and 14-20.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. **Claims 1-12, 14-20 are rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-3 of U.S. Patent No. 6,262,033. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite methods of introducing NFκB decoys into mammalian cells to modulate gene expression for the treatment of ischemic diseases. The patented method to treat ischemic diseases reasonably embrace the instantly recited disease of brain ischemia, wherein the patented method uses a NFκB oligonucleotide decoy composition comprises 100% of the instantly recited nucleic acid sequence, wherein the composition further comprises a pharmaceutically acceptable carrier, e.g. liposome.

22. **Claims 1-12, 14-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting** as being unpatentable over claims 1-4, 7-13 and 16 of EP 0-824-918-A1 (*of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite methods of introducing NFκB decoys into mammalian cells to modulate gene expression for the treatment of ischemic diseases. The patented method to treat ischemic diseases reasonably embrace the instantly recited disease of brain ischemia, wherein the patented method uses a NFκB oligonucleotide decoy composition comprises 100% of the instantly recited nucleic acid sequence, wherein the composition further comprises a pharmaceutically acceptable carrier, e.g. liposome.

Thus, the composition and the method of using said composition as recited in the instant application is reasonably embraced by the claimed composition and methods of using said composition in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. **Claims 1, 5, 7 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting** as being unpatentable over claims 1-2 of copending Application No. 11/324,230.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to NFκB decoys for introduction into mammalian cells, wherein the recited SEQ ID NO:1 in the co-pending application comprises the instantly recited nucleic acid sequence of GGATTTCCC. Thus, the composition as recited in the instant application reasonably embraces the claimed composition in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. **Claims 1-2, 4-12 and 14-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting** as being unpatentable over claims 25-25, 30-31, 33, 35-37, 41, 43-44 and 48 of copending Application No. 10/366,718.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to NFκB decoys for introduction into mammalian cells. The instant claims are drawn to decoy compositions and methods of modulation transcription by introduction of said decoy composition(s) that is a dsDNA molecule that comprises a binding sequence for a transcription factor such that the decoy competitively inhibits binding of the NFκB transcription factor to the gene, thereby treating inflammatory diseases such as rheumatoid arthritis. The conflicting claims in US application 10/366,718 are drawn to compositions and methods of using the NFκB decoys for the treatment of ischemic diseases, which reasonably embrace brain ischemia, in which the NFκB decoy is a linear, double-stranded decoy and comprises the polynucleotide sequence recited in the instant claims, specifically GGATTTCCC.

Thus, the composition and the method of using said composition as recited in the instant application is reasonably embraced by the claimed composition and methods of using said composition in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. **Claims 1, 4-5, 7 and 9-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting** as being unpatentable over claims 1, 3-4, 9 and 11-12 of copending Application No. 10/516,208.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to NFκB decoys for introduction into mammalian cells. The instant claims are drawn to decoy compositions that comprise a dsDNA molecule that comprises a binding sequence for a transcription factor such that the decoy competitively inhibits binding of the NFκB transcription factor to the gene. The conflicting claims in US application 10/516,208 are drawn to compositions in which the NFκB decoy is a linear, double-stranded decoy and comprises the polynucleotide sequence recited in the instant claims, specifically GGATTTCCC.

Thus, the composition as recited in the instant application is reasonably embraced by the claimed composition and methods of using said composition in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

26. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Q. JANICE LI, M.D.
PRIMARY EXAMINER